Atty. Dkt. No. 034536-0928

REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and the following remarks.

It is acknowledged that the amendments are being made after a final rejection, but because the amendments place the application in condition for allowance or in better condition for appeal, without introducing new subject matter or requiring further searching by the Examiner, Applicants respectfully request their entry.

A. Introductory Remarks

Upon entry of the foregoing amendments, claims 17-18, 29, 31, 33, 35-37, 39 and 41 will be pending in the application. Claims 17-18, 29, 31, 33, 35, 37, 39 and 41 are presently being amended. Claims 30, 32, 34, 38 40 and 42 are presently being canceled. No new claims are presently being added. None of the amendments introduces matter into the application

B. The Written Description Supports the Claims

Claims 17-18 and 29-42 were rejected under 35 U.S.C. § 112, first paragraph, because the written description allegedly does not evidence possession of the invention. The Office stated that "[t]he written description in this case only sets forth an isolated antibody or antibody fragment thereof having specific binding affinity to a polypeptide comprising SEQ ID NO: 3 or SEQ ID NO: 4 and a hybridoma which produces an antibody having specific binding affinity to a protein comprising SEQ ID NO: 3 or SEQ ID NO: 4." Such a description allegedly "is not commensurate in scope with the amended claims."

The Examiner suggested that "[t]his rejection could be obviated by amending claims 17-18 to recite '...binding affinity to the AUR1 and/or AUR2...' rather than '...binding affinity to an AUR1 and/or AUR2...". Applicants thank the Examiner for this suggestion, which has been adopted in the foregoing claim amendments.

Claims 17 and 29-36 were further rejected because sufficient description of "enriched" antibodies allegedly does not exist in the specification. Applicants disagree with the rejection, but have deleted "enriched" from the claims to advance prosecution. Accordingly, the rejection is moot.

As the foregoing amendments render the written description rejections moot, Applicants respectfully request withdrawal of the amendments.

C. The Claims Are Patentable over the Cited Art

Claims 17-18 were rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Niwa *et al.*, Gene, 169: 197-201 (1996) ("Niwa") and Campbell, Lab. Tech. Biochem. Mol. Biol., 13: 1-32 (1984) ("Campbell"). According to the Office, Niwa describes a sequence that is an 83.3% match to SEQ ID NO: 3 and which contains spans of more than 40 amino acids that are a 100% match to SEQ ID NO: 3. Campbell allegedly teaches that it is customary for any group working on a macromolecule to make monoclonal antibodies to the macromolecule. Combining these two references, the Office alleges that antibodies having specific binding affinity for AUR1 or AUR2 polypeptides (SEQ ID NO: 3) are obvious. Applicants respectfully traverse the rejection.

The rejection improperly relies on the principle of inherency. In that regard, the rejection asserted that "one of skill in the art would recognize that antibodies raised against Niwa's sequence would have 'specific binding affinity' for a polypeptide encoded by instant SEQ ID NO: 3." At its heart, that is an assertion that antibodies raised against Niwa's polypeptide *inherently* would have specific binding affinity for an AUR1 and/or AUR2 polypeptide encoded by SEQ ID NO: 3. Such is not the case, however.

The legal principle of inherency applies only when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). To establish inherency, it "must [be] clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). In this

context, *necessary* means *always*. For example, in *Glaxo, Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995), one party practiced a prior art method 32 times to obtain the product at issue, but two experts testified that they also had made another product using that same method. Based on this evidence, the appeals court held that the prior art method did not inherently make the product at issue. Thus, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

In the present case, an antibody raised against Niwa's polypeptide would not necessarily bind to a polypeptide encoded by SEQ ID NO: 3, let alone have "specific binding affinity" for a polypeptide encoded by SEQ ID NO: 3. The amino acid sequence of Niwa's polypeptide is only an 83.3% match to SEQ ID NO: 3. Due to the substantial sequence differences, many antibodies raised against Niwa's polypeptide undoubtedly would not bind to a polypeptide encoded by SEQ ID NO: 3. The substantial differences between Niwa's polypeptide and a polypeptide encoded by SEQ ID NO: 3 would alter protein folding, which would result in the two proteins having different conformational epitopes on their surfaces. It is well known that the majority of antigenic determinants on a protein recognized by antibodies are surface conformational epitopes. See Janeway et al. Immunobiology, 5th ed., Garland Publishing, New York 2001, pp. 102-103 (attached). Even if all of the conformational epitopes would not be different, some of them would be and those different conformational epitopes would give rise to antibodies capable of binding to Niwa's polypeptide but not to a polypeptide encoded by SEQ ID NO: 3. With regard to linear epitopes, it is even more apparent that antibodies raised against the polypeptide of Niwa would not necessarily bind to a polypeptide encoded by SEQ ID NO: 3. Any of the sequence differences in Niwa's polypeptide would form linear epitopes not on a polypeptide encoded by SEQ ID NO: 3. Thus, it is not necessarily the case that an antibody raised against Niwa's polypeptide specifically binds to a polypeptide encoded by SEQ ID NO: 3.

Moreover, the Office's allegation that "[o]ne of skill in the art would clearly recognize that antibodies raised against Niwa's sequence would bind to the target (AUR1 and/or AUR2)

polypeptide with greater affinity than they would bind to polypeptides of lesser homology," is pure speculation. If the Office believes that some scientific principle or theory supports the allegation, it must provide evidentiary support for the existence and meaning of that principle or theory. *In re Grose*, 592 F.2d 1161 (CCPA 1979). It has failed, however, to do so.

Because the obviousness rejection improperly relies on the principle of inherency and is unsupported by evidence, it should be withdrawn.

D. The Claims Are Definite

Claims 17 and 29-42 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the rejection stated that there "appears to be no distinct difference between an isolated antibody and a purified antibody." To obviate the rejection, the examiner recommended deleting either "isolated" or "purified" from the claims.

Applicants disagree with the rejection, but have deleted "purified" from the claims to advance prosecution. Accordingly, the rejection is now moot.

Claims 29-34 and 37-42 were further rejected as allegedly being indefinite for reciting "of said AUR1 polypeptide" or "of said AUR2 polypeptide." According to the examiner, a peptide encoded by SEQ ID NO: 3 or SEQ ID NO: 4 is only described as "an AUR1 and/or AUR2 polypeptide," without it being clear which sequence encodes which peptide.

Applicants also disagree with this rejection. It is clear from the specification that SEQ ID NOS: 1 & 3 pertain to AUR1 and that SEQ ID NOS: 2 &4 pertain to AUR2. *See, e.g.*, specification, page 56, lines 19-26 and page 57, lines 9-13. Nevertheless, to expedite prosecution, Applicants have amended the claims to recite "said AUR1 and/or AUR2 polypeptide. Accordingly, the rejection is now moot.

As the foregoing amendments render the indefiniteness rejections moot, Applicants respectfully request withdrawal of those rejections.

Atty. Dkt. No. 034536-0928

E. Concluding Remarks

Applicants believe that this application is in condition for allowance, and request favorable reconsideration of it. If the Examiner believes that an interview would help to advance prosecution, he is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extensions under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 3/16/06

By

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

immunobiology 5

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

Charles A. Janeway, Jr.
Yale University School of Medicine

Paul Travers
Anthony Nolan Research Institute, London

Mark Walport
Imperial College School of Medicine, London

Mark J. Shlomchik
Yale University School of Medicine

GARLAND PUBLISHING
Taylor & Francis Group

Vice President:	Denise Schanck
Text Editors:	Penelope Austin, Eleanor Lawrence
Managing Editor:	Sarah Gibbs
Editorial Assistant:	Mark Ditzel
Managing Production Editor:	Emma Hunt
Production Assistant:	Angela Bennett
New Media Editor:	Michael Morales
Copyeditor:	Lan Ceglelka
Indexer:	Liza Furnival
Illustration and Layout:	Blink Studio, London
Manufacturing:	Marion Morrow, Rory MacDonald

Distributors:
Inside North America: Garland Publishing, 29 West 35th Street, New York, NY 10001-2299.
Inside Japan: Nankodo Co. Ltd., 42-6, Hongo 3-Chrome, Bunkyo-ku, Tokyo, 113-8410, Japan.
Outside North America and Japan: Churchill Livingstone, Robert Stevenson House, 1–3 Baxter's Place, Leith Walk, Edinburgh, EH1 3AF.

ISBN 0 8153 3642 X (paperback) Garland
ISBN 0 4430 7098 9 (paperback) Churchill Livingstone
ISBN 0 4430 7099 7 (paperback) International Student Edition

Library of Congress Cataloging-in-Publication Data
Immunobiology : the immune system in health and disease / Charles A. Janeway, Jr. ... [et al.].– 5th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-8153-3642-X (pbk.)
1. Immunology. 2. Immunity. I. Janeway, Charles. II. Title.

QR181 .I454 2001
616.07'9–dc21

2001016039

This book was produced using QuarkXpress 4.11 and Adobe Illustrator 9.0

Published by Garland Publishing, a member of the Taylor & Francis Group, 29 West 35th Street, New York, NY 10001-2299.

Printed in the United States of America.
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

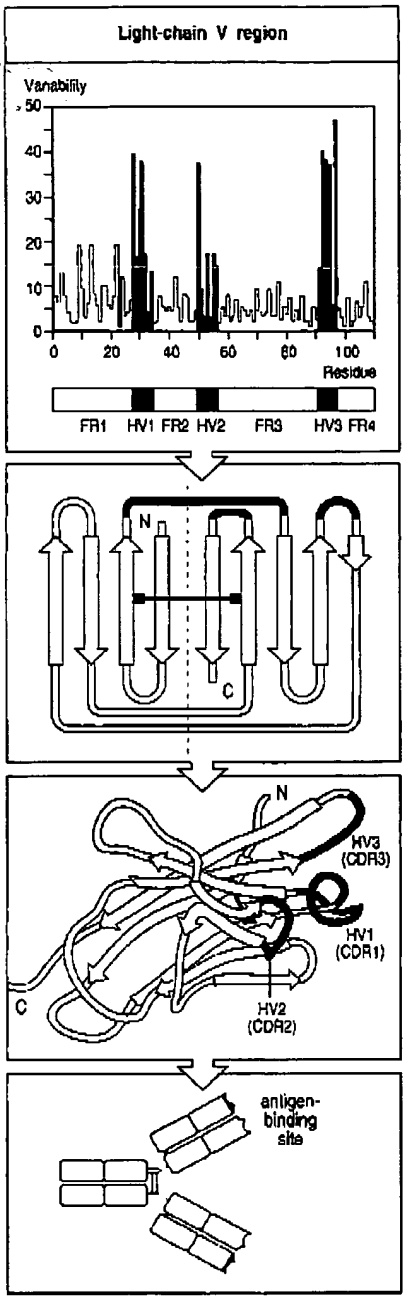

Fig. 3.7 The hypervariable regions lie in discrete loops of the folded structure. When the hypervariable regions (CDRs) are positioned on the structure of a V domain it can be seen that they lie in loops that are brought together in the folded structure. In the antibody molecule, the pairing of a heavy and a light chain brings together the hypervariable loops from each chain to create a single hypervariable surface, which forms the antigen-binding site at the tip of each arm.

found to bind to these antibodies were haptens (see Section 3-4) such as phosphorylcholine or vitamin K_1. Structural analysis of complexes of antibodies with their hapten ligands provided the first direct evidence that the hypervariable regions form the antigen-binding site, and demonstrated the structural basis of specificity for the hapten. Subsequently, with the discovery of methods of generating monoclonal antibodies (see Appendix I, Section A-12), it became possible to make large amounts of pure antibodies specific for many different antigens. This has provided a more general picture of how antibodies interact with their antigens, confirming and extending the view of antibody–antigen interactions derived from the study of haptens.

The surface of the antibody molecule formed by the juxtaposition of the CDRs of the heavy and light chains creates the site to which an antigen binds. Clearly, as the amino acid sequences of the CDRs are different in different antibodies, so are the shapes of the surfaces created by these CDRs. As a general principle, antibodies bind ligands whose surfaces are complementary to that of the antibody. A small antigen, such as a hapten or a short peptide, generally binds in a pocket or groove lying between the heavy- and light-chain V domains (Fig. 3.8, left and center panels). Other antigens, such as a protein molecule, can be of the same size as, or larger than, the antibody molecule itself, and cannot fit into a groove or pocket. In these cases, the interface between the two molecules is often an extended surface that involves all of the CDRs and, in some cases, part of the framework region of the antibody (Fig. 3.8, right panel). This surface need not be concave but can be flat, undulating, or even convex.

3-8 Antibodies bind to conformational shapes on the surfaces of antigens.

The biological function of antibodies is to bind to pathogens and their products, and to facilitate their removal from the body. An antibody generally recognizes only a small region on the surface of a large molecule such as a polysaccharide or protein. The structure recognized by an antibody is called an **antigenic determinant** or **epitope**. Some of the most important pathogens have polysaccharide coats, and antibodies that recognize epitopes formed by the sugar subunits of these molecules are essential in providing immune protection from such pathogens. In many cases, however, the antigens that provoke an immune response are proteins. For example, protective antibodies against viruses recognize viral coat proteins. In such cases, the structures recognized by the antibody are located on the surface of the protein. Such sites are likely to be composed of amino acids from different parts of the polypeptide chain that have been brought together by protein folding. Antigenic determinants of this kind are known as **conformational** or **discontinuous epitopes** because the structure recognized is composed of segments of the protein that are discontinuous in the amino acid sequence of the antigen but are brought together in the three-dimensional structure. In contrast, an epitope composed of a single segment of polypeptide chain is termed a **continuous** or **linear epitope**. Although most antibodies raised

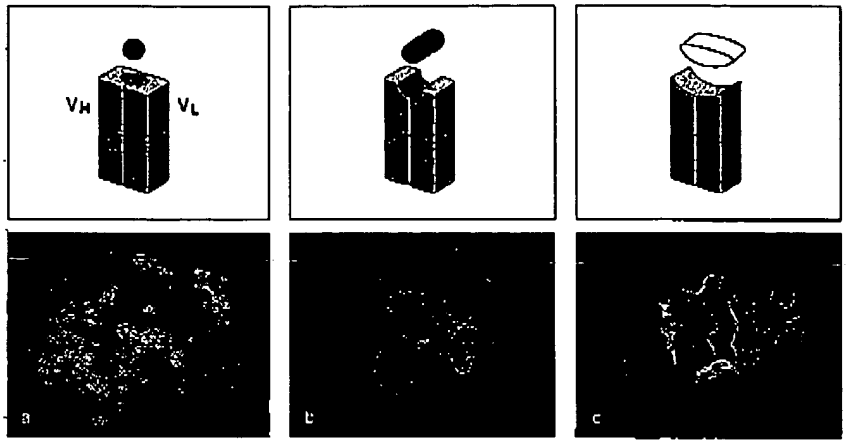

Fig. 3.8 Antigens can bind in pockets or grooves, or on extended surfaces in the binding sites of antibodies. The panels in the top row show schematic representations of the different types of binding site in a Fab fragment of an antibody: left, pocket; center, groove; right, extended surface. Below are examples of each type. Panel a: space-filling representation of the interaction of a small peptide antigen with the complementarity-determining regions (CDRs) of a Fab fragment as viewed looking into the antigen-binding site. Seven amino acid residues of the antigen, shown in red, are bound in the antigen-binding pocket. Five of the six CDRs (H1, H2, H3, L1, and L3) interact with the peptide, whereas L2 does not. The CDR loops are colored as follows: L2, magenta; L3, green; H1, blue; H2, pale purple; H3, yellow. Panel b: In a complex of an antibody with a peptide from the human immunodeficiency virus, the peptide (orange) binds along a groove formed between the heavy- and light-chain V domains (green). Panel c: complex between hen egg-white lysozyme and the Fab fragment of its corresponding antibody (HyHel5). Two extended surfaces come into contact, as can be seen from this computer-generated image, where the surface contour of the lysozyme molecule (yellow dots) is superimposed on the antigen-binding site. Residues in the antibody that make contact with the lysozyme are shown in full (red); for the rest of the Fab fragment only the peptide backbone is shown (blue). All six CDRs of the antibody are involved in the binding. Photographs a and b courtesy of I.A. Wilson and R.L. Stanfield. Photograph c courtesy of S. Sheriff.

against intact, fully folded proteins recognize discontinuous epitopes, some will bind peptide fragments of the protein. Conversely, antibodies raised against peptides of a protein or against synthetic peptides corresponding to part of its sequence are occasionally found to bind to the natural folded protein. This makes it possible, in some cases, to use synthetic peptides in vaccines that aim at raising antibodies against a pathogen protein.

3-9 Antigen–antibody interactions involve a variety of forces.

The interaction between an antibody and its antigen can be disrupted by high salt concentrations, extremes of pH, detergents, and sometimes by competition with high concentrations of the pure epitope itself. The binding is therefore a reversible noncovalent interaction. The forces, or bonds, involved in these noncovalent interactions are outlined in Fig. 3.9.

Electrostatic interactions occur between charged amino acid side chains, as in salt bridges. Interactions also occur between electric dipoles, as in hydrogen bonds, or can involve short-range van der Waals forces. High salt concentrations and extremes of pH disrupt antigen–antibody binding by weakening electrostatic interactions and/or hydrogen bonds. This principle is employed in the purification of antigens using affinity columns of immobilized antibodies, and vice versa for antibody purification (see Appendix I, Section A-5). Hydrophobic interactions occur when two hydrophobic surfaces come together to exclude water. The strength of a hydrophobic interaction is proportional to the surface area that is hidden from water. For some antigens, hydrophobic interactions probably account for most of the binding energy. In some cases, water molecules are trapped in pockets in the interface between antigen and antibody. These trapped water molecules may also contribute to binding, especially between polar amino acid residues.

The contribution of each of these forces to the overall interaction depends on the particular antibody and antigen involved. A striking difference between antibody interactions with protein antigens and most other natural protein–protein interactions is that antibodies possess many aromatic amino acids in their antigen-binding sites. These amino acids participate mainly in van der Waals and hydrophobic interactions, and sometimes in hydrogen bonds. In general, the hydrophobic and van der Waals forces operate over very